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Pharmacokinetic–pharmacodynamic modeling in anesthesia

Pedro L. Gambús [a,*], Iñaki F. Trocóniz[b]

[a]*Department of Anesthesiology, CLINIC Hospital Universitari, Villarroel 170, 08036 Barcelona, Spain*
[b]*Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Navarra, Spain*

Abstract

The so-called "anesthetic state" is a dynamic combination of hypnosis, amnesia, analgesia, neuromuscular and neurohumoral blockade. To achieve this state, different combinations of drug effects must be induced in the patient undergoing the surgical procedure under anesthesia. Patients are routinely and exhaustively monitored during anesthesia. This makes it easy to observe and quantify the effects of anesthetic drugs, and also to attempt to establish the relations between drugs administered, degree of effect and the factors that can influence this relation. Based on the above, important concepts like the "effect compartment model" have been developed. In this case, anesthesia has served clinical pharmacology to describe and validate the concept of the effect compartment. This relation works also in the other way. The effect compartment model has been routinely used to study the profile of different drugs used in anesthesia like opioids (fentanyl, alfentanil, sufentanil and remifentanil), hypnotics (propofol, barbiturates), benzodiazepines (diazepam, midazolam) and neuromuscular blocking agents (pancuronium, vecuronium, atracurium). Based on this approach, it has been possible to develop rational dosing guidelines according to the specific characteristics of the patient for most of the drugs used in anesthesia. More sophisticated modeling techniques, as well as improved designs of clinical trials, made possible to investigate the effect of covariate factors in the PK/PD model. Using this approach has allowed the study of how altered physiologic states as well as the presence of disease can affect the relation between drugs and effect in a particular patient. In addition, different models can be used to study more complex relations like the pharmacokinetics of inhaled anesthetics or the pharmacodynamics of intraspinally administered local anesthetics. The model has been recently described for the interaction between two or three different intravenous agents, enabling the clinician to assess how the use of another drug can influence the effect profile of a given one. Anesthesiology is a very safe medical specialty in terms of morbidity and mortality directly derived from the effect of drugs.

* Corresponding author.
E-mail address: plgambus@menta.net (P.L. Gambús).

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The more we know about the relations between drugs, drug effects and the factors that can affect them, the best it will be for the patients. The application of quantitative modeling in pharmacokinetics and pharmacodynamics enables the clinician to use rationally the anesthetics and, hence, to provide more benefit to the patient undergoing anesthesia.

Keywords: Anesthetics; Drug development; Drug interactions; Modeling; PK/PD

1. Introduction

The goal of clinical anesthesia is to keep the patient stable during the period of surgical stress. This is achieved by combining the administration of drugs to obtain the so-called "anesthetic state", a dynamic combination of different pharmacologic effects: hypnosis, amnesia, analgesia, neuromuscular blockade and blockade of neuro-humoral responses [1]. From a pharmacological standpoint, very few, if any, medical specialties can join together such a different group of powerful, fast and measurable drug effects in a patient that is, routinely, exhaustively monitored. This monitorization enables the quantification of the effect of these powerful drugs on different physiologic systems. The natural consequence is to attempt to establish the relations between amount of drugs given and the different effects induced and measured in anesthetized patients.

Based on the above statements, a strong and synergic relation between anesthesia and clinical pharmacology can be identified, especially when it comes to quantitative pharmacokinetic (PK) and pharmacodynamic (PD) modeling.

On one direction, anesthesia has been the benchmark for the development of new concepts and principles in clinical pharmacology. The most important perhaps, the concept of the "effect compartment" model, was developed in data obtained from experiments where a neuromuscular blocking agent D-tubocurarine was administered, and drug concentrations and drug effect were measured. Data were modeled to integrate and characterize the lag time between the time course of the concentrations of drug and the time course of measured effect [2,3].

The application of pharmacokinetic and pharmacodynamic analysis and the link between them using the "effect compartment model" has proven useful in the other direction. Using PK/PD modeling techniques from the early phases of clinical development has helped to define the characteristics of most drugs specially those intravenously administered. With the appropriate statistical methodology, the effect of covariate factors have been identified and based on all this, rational dosing guidelines have been defined and later on, validated in routine clinical use.

We will describe work that has enabled to define the profile of drugs like remifentanil and propofol. Also, we will present some work were this models are used to describe what happens when anesthetic drugs are given to sick population, how the altered physiology affects the kinetics and dynamics of a drug, how different and more sophisticated models can help to describe what happens not only to intravenously administered but also inhaled

and intraspinally administered drugs. Finally, we will discuss how relevant from a clinical perspective this can be.

2. PK/PD modeling in anesthetic drug development

2.1. Remifentanil

Remifentanil is an opioid analgesic. Its molecule contains an ester linkage that makes it susceptible of being cleaved by the effect of the ubiquitous enzyme plasma and tissue esterases. As a result, its effects (analgesia but also secondary effects like respiratory depression) wear off rapidly after stopping administration, significantly faster than with any other opioid up to date. During the clinical development of remifentanil, several studies were conducted to allow the design of rational dosing guidelines and to assess the possible impact of failure of the elimination organs of the body (liver, kidney) on the offset of effect of remifentanil. Minto et al. studied the pharmacokinetics and pharmacodynamics of remifentanil in a group of 90 healthy volunteers to assess the influence of age and other covariates in both PK and PD. Remifentanil was administered by continuous intravenous infusion, frequent arterial blood sampling was done and the electroencephalographic (EEG) effect was continuously measured. The EEG has been successfully used to study the PD of opioids like fentanyl, alfentanil and sufentanil [4,5]. Nonlinear Mixed Effects Modelling (using the program NONMEM) was used to explore and analyze the data. The high clearance of remifentanil and also the volumes of distribution were influenced by age and other covariate factors. Also, an influence of age was identified in pharmacodynamic parameters. The effect of weight expressed as lean body mass was evident and quantifiable in V1, V2 and Cl1. Age was an important covariate in V1, V2, Cl1 and intercompartmental clearance. In terms of PD parameters, age affected C50 (older people more sensitive to the effects of remifentanil) and also k_{e0} (older individuals would have a slower rate of onset of effect).

Minto et al. [6,7] went a step further. The population approach they used estimated also the interindividual variability. They analyzed if the influence of age as a covariate could be overshadowed by the interindividual variability. A population of 500 young individuals (around 20 years old) and another population of 500 old subjects were generated by the computer. To both groups, the dose of remifentanil that would achieve 50% of maximal EEG effect was administered (single bolus or continuous infusion). If the age effect has been overshadowed by the interindividual variability then, no difference in effect in both groups would have been noted.

Beyond that, other studies confirmed that remifentanil was a safe drug when administered to patients with renal failure as well as those with severe liver damage '8]. Other studies based on simulations have compared the optimal administration scheme with more commonly used opioids like fentanyl or alfentanil [9]. Recently, it has been demonstrated that remifentanil induces acute tolerance to analgesia. Guignard et al. [10], in a clinical study conducted in anesthetized patients, confirmed that the more remifentanil is infused during surgery, the higher the consumption of morphine during the

postoperative period, a finding previously reported by Vinik and Kissin [11] in a group of healthy volunteers under experimental conditions.

2.2. Propofol

Schnider et al. [12] conducted a study to analyze the effect of covariate factors in the PK and PD of propofol. The design involved the administration of a bolus and a short intravenous infusion separated by a washout period. Frequent arterial blood sampling was performed to allow an optimal characterization of the pharmacokinetics of this drug and to identify possible factors that could affect the disposition of this drug. The effect of propofol was measured on the EEG. Clinical endpoints like loss of eyelash reflex or loss of response to verbal command were also measured. This study demonstrated that age and weight had an important role in the disposition of propofol in humans, and also that the PK, after a bolus dose, was different from the PK after a short infusion. The EEG was analyzed using semilinear canonical correlation to extract a parameter, the propofol CUP, maximally correlated with propofol concentration. Based on propofol CUP and also on the clinical responses measured, the value for k_{e0} of propofol, the parameter defining the time lag between plasma and apparent effect site concentrations, was detected. A correct value for k_{e0} will enable delivery systems like de Diprifusor®, a target-controlled infusion system for propofol, to target concentrations either in plasma or in the effect site [13]. The relevance of a correct value for k_{e0} is important. If k_{e0} is not correct, targeting a concentration in the effect site could induce an overdose of propofol in plasma, a situation which will derive in severe secondary effects for the patient like hemodynamic depression [14].

Schuttler recently analyzed the PK of propofol. His group used a population approach to re-analyze data from several studies conducted most of them in a clinical setting and incorporating data from very diverse populations including pediatric patients. Despite the important interindividual variability, the authors came up with a PK model that can be adapted for three different populations: infants, adults and old patients, incorporating the influence of weight in all of the groups [15].

3. Interactions and other applications of PK/PD modeling in anesthesia

The anesthetic state is the net result of combining different pharmacologic effects. To obtain it, usually, several drugs must be combined. It has been already demonstrated how concomitant administration of any combination of say, hypnotic and opioids can influence the other one, either by changing the disposition of one of them like the case of alfentanil and propofol [16], or by changing the effect induced like the case of midazolam and alfentanil [17]. So, in clinical practice, usually, we can diminish the doses of anesthetics because of the synergy that exists between most of the drugs that we use. Other authors like Vuyk et al. [18], Short et al. [19] and Katoh et al. [20] have studied this interactions in an attempt to model the synergy between opioids and hypnotics, being the latter either intravenous or inhalatory.

Using a response surface approach, Minto et al. [21] have addressed also the problem of interactions between anesthetic drugs and have come up with a general, intuitive model that can help in predicting which is the optimal combination of drugs to achieve the effect desired. The relation between drug concentration and effect takes usually the shape of a sigmoid. Between two sigmoids, corresponding to drug A and drug B, lie the sigmoids corresponding to any possible combination of drug A and drug B, each one defined by its own parameters. When looking at all of them at once, the shape of a sigmoidal surface appears. Minto et al. proposed a model where the parameters are estimated as a function of theta, the parameter defining any of the combinations of drugs A and B. Their proposed model, although more mathematically demanding, permits to define the interaction between two drugs at any desired degree of effect and not only in one like the case of the traditional isobolograms.

Another important fact in clinical anesthesia is that the age of the population undergoing surgery is increasing. In a parallel fashion, the number of diseases associated in the patients besides the surgical condition increases as well. In other words, we have older and sicker patients. We have discussed how PK/PD models addressed the age problem by incorporating old individuals in early phase one and two of the clinical development process but, what happens to disease?

Different authors have studied how diseases can change the effect of anesthetic drugs in patients. Our group is conducting a study to characterize the degree of sedation induced by propofol in Parkinson's disease patients undergoing stereotactic surgery to improve their disease. We observed that concentrations of propofol lower than expected for a healthy patient, sedate the patients to the level necessary to go through the whole procedure comfortably [22]. Other authors have observed similar changes but in patients with brain tumors. Whether this can be attributed to PK or PD mechanisms must be elucidated by studies like this one.

Not only prior diseases can affect the behaviour of anesthetics during surgery. A surgical intervention is a dynamic situation where different events can dramatically change the scenario in seconds. For instance, acute bleeding can induce important loss of intravascular fluid containing drug. The reposition of the amount lost will undoubtedly change the distribution of any drug in the body. Animal experimentation has been conducted to address this topic [23]. Changes in homeostatic conditions like hypothermia can affect also the disposition of anesthetic drugs [24].

Sometimes, the principles of compartmental modeling as we are used to apply when it comes to intravenous anesthetics cannot be applied or not in the same way. This is the case, for instance, to establish the relation between intraspinal injection of local anesthetics and the dermatomal level of anesthesia achieved. Intraspinal injection of local anesthetics is a common technique in clinical anesthesia that enables to conduct surgical procedures in the inferior abdomen and lower extremities while keeping the patient conscious or lightly sedated. The modeling approach described by Schnider et al. [25] enabled to characterize this relation and validate it for the case of spinal 0.5% bupivacaine. Our group is trying to use this approach to compare the effects of different local anesthetics and possibly detect the influence of covariate factors like the position of the patient, weight, height, puncture site, adding of opioids, ... in a way that can have some predictive potential [26].

Another case is to apply pharmacokinetic modeling to study the disposition of inhalatory anesthetics. Rietbrock et al. [27,28] have recently come up with a way that permits to study the kinetic properties of this agents. Establishing such a methodology will allow to compare different inhalatory anesthetics in terms of its PK and when combined with an effect measurement like EEG [29,30] to characterize onset and offset of effect. When sufficient data are available, also, it will be possible to identify potential covariate factors that can affect it.

4. Conclusions

Because of its particular characteristics (powerful drugs and measurable drug effects), anesthesia has enabled the development of important pharmacology concepts. The pharmacologic profile of most of the anesthetics used routinely has been developed with the use of PK/PD modeling techniques, and has taken advantage of the population approach to incorporate important covariate factors to tailor the dosing regimens to the specific needs and characteristics of every patient.

There is a need to apply PK/PD modeling techniques to study the interaction and possible synergy between different combinations of anesthetics. It is also important to study how diverse disease states can affect the kinetic and dynamic relations for any anesthetic and the same applies for specific events that can happen during an anesthesia.

Although there is still a lot to do in terms of better knowing the drugs that we currently use and in improving the way we use them, the lack of evidence of a better outcome in anesthetized patients when using one well-established drug instead of a newer more controllable but also more expensive, has shifted the development of new drugs from the field of anesthesia to other areas where more benefits can be obtained.

Appendix A. Discussion 8

K. Wesnes: How do you feel about the opportunity for measuring long-term changes in function, perhaps cognitive function, as a result of anaesthesia, as a clinical 'outcome'? I think it is an area of morbidity, which has not been properly evaluated and might pose some important issues for the research that you are discussing.

P.L. Gambús: There have been some studies in the past addressed to the cognitive function, especially in patients undergoing cardio-pulmonary bypass circulation. It was observed that for a long period of time after surgery, maybe 3 months, there was a decrease at least in the capacity of concentration of these patients. As far as I am concerned, in Europe, there is now an on-going multi-centre study addressing this question for any kind of surgery and different types of anaesthesia. I hope that in the near future, we will see some results being published on this topic because it is something that could really help to demonstrate that using one drug instead of the other can provide a better outcome in terms of cognitive function.

M. Reidenberg: How big an increment does the actual precise calculation of the model give? If I can back off for a minute, certainly, to develop the model, one

needs to have a far better understanding of what the system is and what you're doing than you need without the model. You then have a certain amount of data. When I looked at your surface examples, and Lew's surface examples, there was a big part of that surface that looked pretty similar with different drug doses. The real question that I have is, "is most of this value in making explicit what you are concerned about, and understanding the system?" How much additional information do you get from the precise mathematical calculation related to using the model to get a numerical answer?

P.L. Gambús: Obviously, this model is complex; it is much more complex than using an isobol approximation to this same kind of result, but on the other side, using isobols to some extent limits your appreciation of the interaction to just one, or maybe two degrees...or slices of that surface. If you are able to gather all the number of data and in the number of individuals that would be required, maybe you can gain some insight that is not provided by the isobologram example.

L. Sheiner: In the work that we just saw, and certainly, in the work that I presented, the design of the experiments was almost certainly arrived at long before any modeling occurred. But there is considerable pay-off in thinking about modeling before you design your experiment: you can get a much more efficient design if you do so. Doing so, however, requires thinking, spending time up front rather than afterwards. Regarding the response surface, one may use empirical response surfaces, as here, or mechanistic ones. It seems to me that here is an area where the kinds of models that Dr. Danhof is dealing with might be able to provide additional efficiency, additional extrapolation ability. Because the surface here is empirical, I think, most people would feel a little bit uncomfortable about going off the edges of this model; interpolation is comfortable, but extrapolation may not be.

N. Holford: I do not necessarily agree with what you said about isobole models. They are not actually restricted to the 50%-level for instance, they can apply at any level. There is a family of isobole models that are actually more parsimonious than the polynomial that Charles Minto likes to use. It is extremely empirical. There are somewhat less empirical isobole models that probably fit that family of surfaces with fewer parameters. But on a more positive note, I think, the application of this kind of response surface modeling is to the robot anaesthetist—basically to put you out of business, you just drive the computer, the computer drives the patient. Would you like to comment on the successes of modeling for robot anaesthetists?

P.L. Gambús: There is a trend in using closed-loop systems to control anaesthesia, and the present state of this kind of research is that there is not still a well-defined measure of hypnotic effect, which is where it has been the most amount of work. There are some indices derived from the EEG that has been used and are currently in development, but there are also some intervals during surgery where the degree of artifacts is so important that the closed-loop system should be transformed into an open-loop system. The anaesthesiologist does the arrangements by himself, so, I do not think this is a well-resolved topic nowadays. We will still need for either a better way to get rid of all these artifacts, or a better way of measuring the effect of anaesthetics, because at least, in the case of hypnotics, we are using surrogate measures that can have some pros and cons also.

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