Towards an ideal PK-PD Model. A study with myasthenic models and muscle relaxants.
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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When a patient needs general anesthesia for a surgical procedure, there are certain requirements with which anesthesia must comply. Patients must be properly anesthetized using hypnotics and analgesics. Also, muscle relaxation is required for intubation and for abdominal or intrathoracic surgery. Muscle relaxation prevents surgery-related increases in muscle tone. Volatile anesthetics influence the degree and time course of effect of neuromuscular blocking agents. The function of important clearing organs, like kidney and liver, and diseases of the neuromuscular system, like myasthenia gravis, also influence the requirement for neuromuscular blocking drugs.

Patients with myasthenia gravis are more sensitive to muscle relaxants. This is thought to arise from a decreased acetylcholine receptor concentration at the neuromuscular junction. The neuromuscular junction, which is the effect compartment for neuromuscular blocking agents, is selectively affected. Therefore the myasthenic state offers unique possibilities to study the potency and time course of effect of neuromuscular blocking agents, because. The main goal of this study was to find a pharmacokinetic-pharmacodynamic (PK-PD) model that would provide a better understanding of the biophase kinetics, and particularly of the role of receptor density in the pharmacology of neuromuscular blocking agents. Ultimately this may lead to a safer and more rational use of neuromuscular blocking agents.

Chapter I gives a general overview of the anatomy and physiology of the neuromuscular junction. The mechanisms underlying neural activation of a muscle are explained. The anatomy of the prejunctional nerve terminal, of the synaptic cleft and of the postjunctional muscle cell membrane is described. Also the physiology of neuromuscular transmission is reviewed, with respect to acetylcholine synthesis and storage and release of acetylcholine following the arrival of an action potential at the nerve terminal and the activation of the endplate leading to muscle contraction. The section on pharmacology describes drugs with prejunctional effects, drugs that have postjunctional effects, and drugs that have combined effects, like neuromuscular blocking agents and anticholinesterases. Methods of quantification of the degree of neuromuscular transmission are mentioned. The last part of this chapter reviews some dysfunctional states of the neuromuscular junction, caused by diseases like (congenital) myasthenia gravis and the Lambert Eaton myasthenic syndrome, by poisoning with organophosphorous agents or animal toxins, and by the presence of atypical plasma cholinesterase.
Chapter II deals with the backgrounds of pharmacokinetic-pharmacodynamic modeling. The relatively complex physiological modeling approach as well as the more simple mathematical compartmental modeling approach are reviewed. Population pharmacokinetics and different methods to model population data are summarized. Combining pharmacokinetics and pharmacodynamics offers the opportunity of PK-PD modeling. The gold standard, i.e. the link model proposed by Sheiner and colleagues, is presented and circumstances are discussed under which this model is unable to predict the time course of effect of neuromuscular blocking agents adequately. Three examples are presented to illustrate the shortcomings of the Sheiner model i.e., the poor prediction during the first minutes after administration of a neuromuscular blocking agent, the inappropriateness to model a mivacurium-induced block, and the inability to predict the PK-PD in myasthenia gravis. Finally, a new PK-PD model, i.e. the unbound receptor model, is introduced and its performance in myasthenic PK-PD modeling is examined. The results are compared to those obtained with another PK-PD model, taking into account the receptor concentration, the model proposed by Donati and colleagues.

Chapter III connects the introductory part to the experimental part, placing the conducted studies in the context of this thesis.

Chapter IV describes the development of a new animal model, that enables studying the biophase kinetics of neuromuscular blocking agents. This new model should provide a way to study the pharmacodynamics of neuromuscular blocking agents with minimal interference of pharmacokinetic events. The tibialis anterior muscle of a rat was dissected free from the other muscles of the hind leg and the distal end was connected to a force transducer, after which the skin was closed again to prevent heat and fluid loss. The arterial and venous blood vessels were cannulated to provide a single pass perfusion of the tibialis muscle with rat donor blood. The tibialis nerve was prepared free from the surrounding tissues and connected to a nerve stimulator. During the experiment, the rat was placed in a heated, thermostatically controlled chamber. To test this model for viability, blood samples taken after perfusion were examined, histological samples were reviewed and the response of the muscle to nerve stimulation was monitored. In this chapter, also results are reported of some preliminary experiments with neuromuscular blocking agents which differ in potency, and experiments with different flow rates. After a stabilization period, an infusion with rocuronium or pancuronium was started, until a stable neuromuscular block of 90% was obtained. The infusion was then turned off. The time
course of effect of the neuromuscular blocking agent was recorded and analyzed. It was found that the potency of a neuromuscular blocking agent had little or no influence on the onset and offset of the neuromuscular block, while a higher blood flow to the muscle speeded up the rate of both onset and offset of neuromuscular block. This is in contrast to findings in in vivo studies in animals and humans. The difference between the rate of onset or offset with higher flow illustrates the decisive role of pharmacokinetics on the time course of effect of neuromuscular blocking agents in vivo.

In chapter V, this tibialis anterior model in rats is used to study the influence of a decreased acetylcholine receptor concentration on the time course of effect of neuromuscular blocking agents. Two different myasthenic rat models were used. The first model was an acute myasthenic model, in which alpha-bungarotoxin was used to simulate a decreased acetylcholine receptor state. Alpha-bungarotoxin binds irreversibly to the majority of acetylcholine receptors, decreasing the number of acetylcholine receptors available for acetylcholine and neuromuscular blocking agents at the neuromuscular junction. Also a more chronic model of myasthenia gravis was used. Rats showed clinical features of myasthenia after anti-bodies against the acetylcholine receptor had been used. This could be confirmed by laboratory analysis, comparing the acetylcholine receptor concentration of tibialis anterior muscles of control rats and myasthenic rats. An infusion with pancuronium or rocuronium was started until a stable 90% block was reached and the time course of effect was recorded. The recorded data were analyzed using PkPdFit. Different PK-PD models were used. Finally, the link model proposed by Sheiner and colleagues was compared to a new PK-PD model, that takes into account the number of acetylcholine receptors available for neuromuscular transmission. The latter model was found to be more suitable to describe the observed changes in time course and potency in these 'myasthenic' rats. Using PK-PD modeling, a decrease in $EC_{50}$ could be demonstrated, as reflected by the increased sensitivity and a less steep concentration-effect relationship.

Chapter VI describes the development of a model for myasthenia gravis in pigs, to test this new PK-PD model in a setting that would allow drawing blood samples. Pigs were injected intramuscularly with the acetylcholine receptor of the Torpedo californica (pacific electrical ray) and received a second injection (boost) 21 days later. All pigs became myasthenic within a week following the second injection. They showed loss of appetite and food intake, and clinical signs of muscle weakness. During the PK-PD
Towards an ideal PK-PD model

modeling study, rocuronium was infused at a slow rate, both in myasthenic and in healthy control pigs, to obtain a 90% neuromuscular block. At predefined time points, blood was sampled to determine the rocuronium concentration. A PK-PD analysis was performed, using the Sheiner model and the unbound receptor model. Analysis revealed that solely a decrease in receptor concentration could describe the observed differences in rocuronium time course of effect in myasthenic pigs, when compared to control pigs. The transport rate constant from the first compartment to the effect compartment was different between control pigs and myasthenic pigs. This may be attributable to a relatively hypovolemic state and a concomitant decreased cardiac output in myasthenic pigs when compared to control pigs. Pharmacokinetic parameters were the same in both animal groups.

In chapter VII, a PK-PD modeling study in humans was conducted, and the performance of the unbound receptor model in humans was examined. Eight myasthenic patients were studied, who were scheduled for thymectomy and eight control patients, scheduled to undergo elective ear nose and throat surgery or general surgery not requiring additional relaxation after intubation. Rocuronium was administered by a short infusion at a predefined rate to reach a neuromuscular block of at least 90% in both control and myasthenic patients. The rate in the latter group was reduced to compensate for a decreased requirement (25 μg/kg/min in myasthenic patients versus 116.7 μg/kg/min for control patients). At predefined points during onset and offset of neuromuscular block, arterial samples were taken. Data were analyzed with both the link model proposed by Sheiner and the unbound receptor model. Contrary to our findings in myasthenic pigs, solely a decrease in receptor concentration could not provide a reasonable fit for data obtained in these myasthenic patients. The exponential coefficient of the relationship between the twitch height and the receptor concentration in myasthenic patients had to be adjusted compared to that of controls. This different exponential coefficient might be linked to interindividual differences in the treatment of myasthenia gravis. The unbound receptor model was able to provide a better fit of the time course of effect in myasthenic patients and a reasonably good fit in control patients.

Finally, in chapter VIII, we used the obtained PK-PD values to simulate the behavior of a closed-loop infusion system, based on a proportional-integral-constant (PI+C)-controller in myasthenic patients. Based on a measured variable for degree of paralysis the closed-loop infusion system administers a muscle relaxant (in this case rocuronium) to a patient, in an
effect-controlled manner (i.e. to a degree of neuromuscular block). In this case a PIC-controller and twitch height after single twitch stimulation were used to keep neuromuscular block at a predefined level. A controller was designed for normal patients and myasthenic patients (both based on the Sheiner and the Unbound Receptor model). The performance of each controller was tested in both control and myasthenic patients. The parameter set (control or myasthenic patients) as well as the PK-PD model (Sheiner or Unbound Receptor) that were used to optimize such a controller have only limited effect on the performance of the controller. The performance of a PIC controller is good, regardless of the PK-PD model that is used, or the patient group for which the controller is optimized.

It was concluded that the unbound receptor model is a useful model to be applied in myasthenic patients or in the various animal models. If the study is conducted in homogeneous groups (chapter IV and chapter V), the unbound receptor model performs better than the Sheiner model. The unbound receptor model relates the observed time course of effect to the acetylcholine receptor concentration. Furthermore, the model improves the fitting results for data obtained in myasthenic patients. It does, however, not improve PK-PD fitting in control patients. The major advantage of this model is that it explains the observed changes in time course of effect and potency of neuromuscular blocking agents in a more physiological way than the Sheiner model. In the latter model, the increased sensitivity can be accounted for by decreased model parameters, such as gamma and effective concentration at 50% effect, but there is no explanation as to why these parameters are decreased. The unbound receptor model offers an explanation for the observed changes in time course and potency in myasthenic patients, based on the decreased acetylcholine receptor concentration, that is seen in myasthenic patients. The unbound receptor improves the PK-PD fitting results, regardless of how the reduction of acetylcholine receptor concentration has been reached.

It may be interesting to test the unbound receptor model in burn patients, which have an up-regulated number of acetylcholine receptors. The up-regulation increases both junctional and extrajunctional receptors, and the majority of the up-regulated receptors are of the fetal type which goes together with different binding, conducting and opening time characteristics. It should be clear that only the junctional up-regulation may be reflected in the unbound receptor model, whereas an increase of the extrajunctional receptors will only influence the dose requirement.