Kinship and interaction in neuromuscular pharmacology

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Summary

Introduction
The background of this thesis is presented in the introductory chapters and starts with a brief history of neuromuscular relaxants. It is followed by a short description of the neuromuscular physiology and pharmacology in chapters 2 and 3, respectively. In chapter 4 the aim of the thesis is presented:

> *To investigate the dose-concentration-effect relationship of some non-depolarising muscle relaxants and their interactions.*

Scientific studies
In *chapter 5* the pharmacodynamics of vecuronium are compared to those of rapacuronium (Org 9487). The time course of action of equipotent doses of rapacuronium and vecuronium is measured. Also their mutual interaction when given in succession is investigated. Sixty ASA I-II patients were anaesthetised with thiopentone, fentanyl, halothane and nitrous oxide and assigned randomly to four groups. Each patient received an initial dose of either vecuronium or rapacuronium followed by maintenance doses of either vecuronium or rapacuronium (initial dose/maintenance dose: rapacuronium/rapacuronium, vecuronium/rapacuronium, rapacuronium/vecuronium and vecuronium/vecuronium). The time course of action was measured mechanomyographically, determining the duration of the single twitch until 25% recovery (DUR_{25}). The onset time of an initial dose of rapacuronium was shorter than that of an initial dose of vecuronium [96 and 203 sec, respectively; $P<0.001$]. The DUR_{25} of the initial dose of rapacuronium was less than half that of vecuronium [10.7±2.8 and 28.8±6.1 min, respectively; $P<0.001$]. The DUR_{25} of the first and second maintenance doses of rapacuronium were shorter than those of vecuronium (rapacuronium/rapacuronium: 7.3±2.8 and 8.5±2.4 min; vecuronium/rapacuronium: 12.7±3.3 and 11.5±3.5 min, vs rapacuronium/vecuronium: 16.4±4.5 and 20.6±4.7 min; vecuronium/vecuronium: 18.8±3.0 and 20.1±3.8 min, respectively; $P<0.05$). An initial dose of vecuronium prolonged the DUR_{25} of the first and second maintenance doses of rapacuronium significantly ($P<0.05$). In the rapacuronium/rapacuronium group an individual increase in DUR_{25} was observed with increasing maintenance dose administration.
From these results it can be concluded that rapacuronium is a muscle relaxant with a shorter onset time and shorter duration of action than vecuronium. Maintenance doses of rapacuronium are also shorter acting than equipotent maintenance doses of vecuronium, irrespective of which relaxant is given initially.

In *chapter 6* the pharmacokinetic behaviour of the 3-desacetyl metabolite of rapacuronium, Org 9488, is investigated in man (n=7). Additionally, in two separate studies the pharmacokinetic-pharmacodynamic (PK-PD) relationship of rapacuronium (n=10) and Org 9488 (n=7) were investigated. The reason to study this is that the 3-desacetyl metabolite of rapacuronium, Org 9488, also exerts neuromuscular blocking activity. This may become apparent after prolonged maintenance of relaxation with rapacuronium. Investigation of the PK-PD relationship of both rapacuronium and its metabolite may offer some insight in how they interact at the effect site.
Similar protocols were used for three study groups regarding the anaesthetic technique, blood and urine sampling, pharmacokinetic and PK/PD analysis. The time course of action was measured mechanomyographically at the adductor pollicis muscle. The median clearance of rapacuronium was 7.28 $ml.kg^{-1}.min^{-1}$ with an excretion fraction in the urine of 6.2%. The clearance of Org 9488 (studied in two groups) was 1.28 and 1.06 $ml.kg^{-1}.min^{-1}$ with an excretion fraction in the urine of 51.9% and 53.5%, respectively. The median rate constant of transport between plasma and the biophase (k_{e0}) of rapacuronium (0.449 min^{-1}) is markedly

larger than for Org 9488 (0.105 min^{-1}). The modeled concentration in the biophase at 50% effect (EC_{50}) as a measure of potency is higher for rapacuronium (4.70 $\mu g.ml^{-1}$) than for Org 9488 (1.83 $\mu g.ml^{-1}$). It is concluded that the clearance, k_{e0} and EC_{50} of rapacuronium are consistent with its rapid onset and short to intermediate duration. The lower clearance of the metabolite will gradually prolong the time course of the neuromuscular blockade during maintenance with rapacuronium.

In *chapter 7* the PK-PD data of vecuronium, rapacuronium and their active metabolites were used to simulate the interaction between vecuronium and rapacuronium. These results were used for comparison to the data from the clinical, experimental, pharmacodynamic study presented in chapter 5. The information from these simulations may contribute to the identification of the type of interaction. Hypothetically the type of interaction is said to have an additive character.
The clinical study results from chapter 5 and 6 are used. PK-PD data of vecuronium were taken from a published study and personal communication with the investigator of this study (Prof. Caldwell, San Francisco).
The DUR_{25} of a maintenance dose as described in chapter 5 (DUR_{25}) was recalculated as a percentage of the mean DUR_{25} of the initial dose to account for interindividual differences. A modification of Sheiner's method was used for PK-PD modeling. Simulations were performed by the computer program PKPD to describe the concentration-time profile in the compartments, including the effect compartment, and the time course of neuromuscular block. The simulations reproduced the experimental results satisfactorily. Especially in the group rapacuronium/rapacuronium DUR_{25} could only be simulated satisfactorily if the influence of the active metabolite of rapacuronium, 3-desacetyl-rapacuronium (Org 9488), was taken into account. The contribution of the active metabolite of vecuronium, 3-desacetyl-vecuronium (Org 7268), was much less pronounced.
The hypothesis that the interaction between muscle relaxants of the same group, i.e. aminosteroids, is additive, is supported by the results of this simulation study. The time course of action of combinations of rapacuronium and vecuronium may be explained by their PK-PD characteristics. The active metabolite of rapacuronium influences the time course of action to a greater extent than the active metabolite of vecuronium.

In *chapter 8* the PK-PD relationship of the three mivacurium isomers (*cis-cis, cis-trans,* and *trans-trans)* and their interaction are investigated. In particular, the time course of action of mivacurium does not correlate with its rapid breakdown by plasma cholinesterase.
Fourteen patients between 25-55 years, undergoing non-major surgery, ASA class I-II, were included. All patients received thiopentone/fentanyl/isoflurane/O_2/N_2O anaesthesia. Neuromuscular block was monitored mechanomyographically using single twitch stimulation (0.1 Hz). Mivacurium was administered as a short-term infusion, mean (SD) duration 4.7 (1.0) min and dose 145 (33) $\mu g\ kg^{-1}$. Arterial blood samples were obtained, and plasma was analysed by high performance liquid chromatography. Pharmacokinetic and PK-PD modeling was performed using an iterative two-stage Bayesian approach, assuming that the *trans-trans* and *cis-trans* isomers are equally potent.
A PK-PD model with an effect compartment linked to plasma did not fit to the data satisfactorily. A model using an interstitial space compartment between plasma and effect compartment fitted significantly better. Parameters [mean (%CV)] of the best fitting model were: k_{ip} 0.374 min^{-1} (46%), k_{ei} 0.151 min^{-1} (36%), EC_{50} 98 $\mu g\ L^{-1}$ (29%), and γ 3.7 (22%). It is concluded that the PK-PD behaviour of mivacurium could be described using a model with an interstitial space compartment interposed between the plasma and effect compartment. This model shows that the time course of mivacurium is governed mainly by

the concentration decline in this interposed compartment and only indirectly related to the rapid plasma clearance.

In *chapter 9* different strategies to analyse PK-PD data are investigated.
Usually pharmacokinetic-pharmacodynamic (PK-PD) modeling is performed sequentially: first the pharmacokinetic (PK) model parameters are estimated from the plasma concentration data (PK analysis); then the parameters of the link model (if applicable) and the pharmacodynamic model are estimated from the effect measurements and the PK parameters (PD analysis). This approach is not ideal from a statistical point of view, because the estimated PK parameters are treated as error-free constants in the PD analysis. These statistical concerns may be satisfied using simultaneous PK-PD analysis of individual data by maximisation of the joint likelihood of the PK and PD parameters. A method for simultaneous PK-PD population analysis was developed using an Iterative Two-Stage Bayesian algorithm and this technique was evaluated using clinical data of rocuronium as well as Monte Carlo simulations.
Eleven patients (ASA class I-III) undergoing non-major surgery, aged between 20-64 years, received thiopentone-fentanyl-isoflurane-O_2-N_2O anaesthesia. Neuromuscular block was monitored mechanomyographically with single twitch stimulation (0.1 Hz). Rocuronium was administered as a short-term infusion, mean (SD) duration 5.1 (1.0) min and dose 414 (89) $\mu g.kg^{-1}$. Arterial blood samples were obtained and plasma was analysed by high performance liquid chromatography.
PK-PD parameters were estimated from nine evaluable patients by sequential analysis, PD analysis from nonparametric PK data, and simultaneous analysis. Both Standard Two-Stage analysis and Iterative Two-Stage Bayesian analysis were used for population analysis.
The design of the Monte Carlo simulation study was similar to that of the clinical study. In total 1,000 population data sets of 9 patients each were generated by Monte Carlo simulation. The accuracy and precision of the estimated model parameters were evaluated by comparing their mean error and root mean squared error. Also the influence of the PD model misspecification on the results was investigated.
The PK-PD population parameters and their interindividual variability were markedly different between methods. In the Monte Carlo simulation, Iterative Two-Stage Bayesian analysis performed better than Standard Two-Stage analysis. The simultaneous PK-PD analysis resulted in slightly more precise population parameter estimates than the sequential PK-PD analysis and the nonparametric PK method. In the presence of PD model misspecification, simultaneous analysis resulted in poor PK parameter estimates, while sequential PK-PD analysis performed better.
It is concluded that Iterative Two-Stage Bayesian analysis is a valuable technique for PK-PD population analysis, and is superior to Standard Two-Stage analysis . Simultaneous PK-PD analysis using Iterative Two-Stage Bayesian analysis was the most accurate and precise method. However, in the presence of model misspecification the simultaneous analysis may provide poor PK estimates. Therefore, the sequential PK-PD method using Iterative Two-Stage Bayesian analysis is more suited for the analysis of real data.

In *chapter 10* general conclusions are made and future perspectives discussed.
Towards the ideal time course of neuromuscular blockade during surgery, combinations of muscle relaxants are investigated and newer muscle relaxants have been developed. Interaction between pharmacologically active molecules at the acetylcholine receptor of the neuromuscular junction may occur as muscle relaxants are administered as mixtures of isomers (kinship grade 1), transformed into active metabolites (kinship grade 2) or given in a combination of muscle relaxants (kinship grade 3 and 4).

PK-PD analysis provides proper information about the dose-concentration-effect relationship of these muscle relaxants and their mutual interaction. A sequential Bayesian PK-PD analysis is the preferred strategy.
Nowadays not a single muscle relaxant is available that meets the criteria of rapid onset and flexible duration of action without unwanted effects. The aminosteroidal muscle relaxant rocuronium offers an acceptable alternative if a non-depolarising rapid onset is preferred.
A flexible duration of action after rocuronium administration may be created only by the specific rocuronium antagonist, sugammadex. Sugammadex, a γ-cyclodextrin, inactivates free rocuronium molecules by encapsulation and is currently under clinical investigation.